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Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: A plea for implementation of early switch and early discharge criteria

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ABSTRACT

This retrospective observational medical chart review aimed to describe country-specific variations across Europe in real-world meticillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft-tissue infection (cSSTI) treatment patterns, antibiotic stewardship activity, and potential opportunities for early switch (ES) from intravenous (i.v.) to oral formulations and early discharge (ED) from hospital using standardised data collection and criteria and economic implications of these opportunities. Patients were randomly sampled from 12 countries (Austria, Czech Republic, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Slovakia, Spain and the UK), aged ≥18 years, with documented MRSA cSSTI, hospitalised between 1 July 2010 and 30 June 2011, discharged alive by 31 July 2011. Of 1502 patients, 1468 received MRSA-targeted therapy. Intravenous-to-oral switch rates ranged from 2.0% to 20.2%, i.v. length of therapy from 10.1 to 18.6 days and hospital length of stay (LoS) from 15.2 to 25.0 days across Europe. Of 341 sites, 82.9% had antibiotic steering committees, 23.7% had i.v.-to-oral switch antibiotic protocols and 12.9% had ED protocols for MRSA cSSTI. ES and ED eligibility ranged from 12.0% (Slovakia) to 56.3% (Greece) and from 10% (Slovakia) to 48.2% (Portugal), respectively. Potential cost savings per ED-eligible patient ranged from €414 (Slovakia) to €2703 (France). MRSA cSSTI treatment patterns varied widely across countries, but further reductions in i.v. therapy, hospital LoS and associated costs could be realised. These data provide insight into clinical practice patterns across diverse European healthcare systems and identify potential opportunities for local clinicians and policy-makers to improve clinical care and cost-effectiveness of this therapeutic area.

1. Introduction

European healthcare systems are under increasing economic pressure, with greater demand to provide care despite stable or declining budgets [1]. The percentage of patients aged ≥80 years is projected to increase (4.4% in 2008, 8% in 2035, 12.1% in 2060),

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whilst the number of hospital facilities and beds in Europe will likely decrease [2]. This underscores the need for programmes that can enable hospitalised patients to continue treatment in outpatient settings with few negative impacts.

Outpatient parenteral antibiotic therapy (OPAT) programmes enable patients to receive intravenous (i.v.) antibiotics after hospital discharge but require additional resources and are not available to all patients in Europe [3–5]. Early switch (ES) programmes promote switching patients from i.v.-to-oral antibiotic therapies, and early discharge (ED) programmes enable patients to finish treatment after hospital discharge. ES and ED programmes are beneficial [6–10], require few additional resources and are considered relatively low cost and high impact antimicrobial stewardship strategies [11]. These programmes are regarded as having the greatest potential benefit for the management of meticillin-resistant *Staphylococcus aureus* (MRSA) infections, particularly complicated skin and skin-structure infections [7,12]. Clinical trial data in MRSA complicated skin and soft-tissue infection (cSSTI) have suggested longer length of stay (LoS) in Europe compared with other world regions owing to different healthcare systems and incentives [13].

Variations have been reported in ambulatory use of antibiotics and hospitalised respiratory infections [6,7]; however, little is known about variations in real-world MRSA cSSTI treatment patterns in hospitals across different European countries. Given limited pan-European data on real-world practice patterns for treatment of MRSA cSSTI as well as expected economic pressures to optimise available resource use, a retrospective observational study was conducted using consistent methodology across 12 European countries. The objectives were: (i) to illustrate cross-country variations in practice patterns for MRSA cSSTI treatment, including initiation of therapy, choice of drugs, treatment regimen changes, and duration of therapy and hospitalisation; (ii) to assess current availability and impact of hospital antibiotic drug use policies; (iii) to describe potential opportunities for ES and ED by application of standardised criteria across countries; and (iv) to demonstrate the potential economic impact of ES and ED programmes at the country level. These data may provide insight into clinical practice patterns across diverse European healthcare systems and may help identify opportunities to improve the efficiency of patient care.

2. Methods

A retrospective observational medical chart review was conducted including 12 European countries: Austria, Czech Republic, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Slovakia, Spain, and the UK. The complete methods will be published in a forthcoming paper. Study investigators [hospital-based infectious diseases (ID) specialists, internists with an ID subspecialty and medical microbiologists] identified patients for data collection.

Included patients were: hospitalised between 1 July 2010 and 30 June 2011 inclusive and were discharged alive by 31 July 2011; were aged ≥18 years; had a confirmed MRSA cSSTI (e.g. deep/extensive cellulitis, infected wound or ulcer, major abscess or other soft-tissue infection requiring substantial surgical intervention); and received ≥3 days of i.v. anti-MRSA antibiotics. Patients were excluded if they: were treated for the same SSTI ≤3 months from hospitalisation; had suspected or proven diabetic foot infection, osteomyelitis, infective endocarditis, meningitis, joint infection, necrotising fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection; were pregnant or lactating; had significant concomitant infection at other sites (e.g. bacteraemia, pneumonia); were immunosuppressed (e.g. diagnosed with haematological malignancy or rheumatoid arthritis, neutropenic, undergoing cancer chemotherapy, receiving chronic steroids); or were enrolled in another cSSTI-related clinical trial.

2.1. Study populations

The main study population included patients whose medical charts were randomly selected by study investigators so that the population accurately reflected practice patterns of each country. A limited number of patients received treatment with questionable or suboptimal coverage for MRSA. Thus, a subgroup was identified who received a confirmed MRSA-active antibiotic with a labelled or guideline indication for MRSA cSSTI or with anti-MRSA activity confirmed by susceptibility tests [e.g. i.v. chloramphenicol, i.v./oral clindamycin, i.v. daptomycin, i.v./oral doxycycline, i.v. fosfomycin, i.v./oral fusidic acid, i.v. lincomycin, i.v./oral linezolid, oral minocycline, i.v. netilmicin, i.v. norfloxacin, i.v. quinupristin/dalfopristin, i.v./oral rifampicin, i.v./oral trimethoprim/sulfamethoxazole, i.v. teicoplanin, i.v. tigecycline, oral trimethoprim and i.v. vancomycin]. The following antibiotics were considered MRSA-active after reviewing wound cultures for MRSA sensitivity: i.v./oral ciprofloxacin; i.v. ertapenem; i.v. imipenem; i.v./oral levofloxacin; i.v. meropenem; i.v./oral moxifloxacin; and oral ofloxacin. Owing to limited recruitment, patients from Ireland contributed to the overall cohort but their results are not presented separately.

2.2. Key outcomes

2.2.1. Hospital-level organisation and protocols for antibiotic use and early discharge

A separate hospital-level information form collected site data on the presence of antibiotic subcommittees and drug use policies for i.v.-to-oral antibiotic switching or ED. These data were summarised by country to understand existing country-level systems at the time of the study to address i.v.-to-oral antibiotic switching and ED.

2.2.2. Meticillin-resistant S. aureus-active antibiotic treatment patterns

Patient-level first and last MRSA-active therapies administered in hospital as well as MRSA-active therapies prescribed at discharge (including drug and administration pattern) were determined overall and by country. Administration patterns evaluated included i.v. only, i.v.-to-oral antibiotic switch and discharge on antibiotics (i.v./intramuscular or oral).

2.2.2.1. Actual length of intravenous therapy and hospital length of stay. Length of i.v. therapy and LoS were determined overall and for each country. Length of i.v. therapy was defined as the time between start of MRSA-active i.v. treatment and last date of inpatient i.v. antibiotic use. LoS was measured from hospital admission for patients admitted for treatment of MRSA cSSTI, from the date of cSSTI diagnosis (cSSTI index date).

2.2.2.2. Early switch and early discharge opportunities. To explore possible resource utilisation reductions, potential for ES (sooner than patients actually discontinued their MRSA-active i.v. antibiotics) and for ED (earlier than actual discharge date on oral antibiotics or through an OPAT programme) were evaluated. ES and ED criteria were developed through literature review [3–10] and expert consensus opinion. ES eligibility required patients to meet all of the following criteria before i.v. discontinuation: stable clinical infection; afebrile/temperature <38 °C for 24 h; white blood cell count normalised or not $<4 \times 10^9$/L or $>12 \times 10^9$/L; no unexplained tachycardia; systolic blood pressure ≥100 mmHg (for OPAT); and oral fluids/medications/diet tolerated with no gastrointestinal absorption problems. ED eligibility required meeting all of the above criteria for ES before discharge and having no reason to remain hospital except for infection management.

To understand the impact ES and ED eligibility could have on resource utilisation, potential i.v. days saved due to ES eligibility were calculated as excess days between the time the patient became eligible and when they actually discontinued i.v. therapy. Potential bed-days saved due to ED eligibility were calculated as excess days between the time patients became eligible and when they were actually discharged. The potential economic benefit of LoS reductions was calculated by multiplying potential bed-day savings by country-specific World Health Organization-reported unit costs (international dollars) for a hospital bed-day in 2008 (Appendix) [14]. Unit costs were adjusted for inflation to 2012 and were converted to euros [15,16]. Costs were applied at a patient level (e.g. person-level bed-days saved × cost per bed-day).

2.3. Statistical analysis

Categorical variables were summarised as frequencies and percentages and continuous variables as the mean and standard deviation (S.D.). To test for differences between groups, Pearson's χ^2 test for categorical variables and Student's *t*-test or analysis of variance for continuous variables were used. For the analyses: (i) all patients in the main cohort were used to describe demographic and disease characteristics, ES and ED eligibilities, and actual hospital LoS; (ii) the subset receiving MRSA-active treatment was used for MRSA-active antibiotic treatment patterns and i.v. therapy days; and (iii) the subsets who were eligible for ES or ED were used to describe the potential savings in i.v. days or hospital LoS, respectively. At a country level, correlations and their statistical significances were evaluated between the proportion of sites having an antibiotic subcommittee and i.v.-to-oral antibiotic switch or ED protocols and the proportion of patients observed to switch from i.v. to oral antibiotics, mean i.v. days and mean LoS. All inferences assumed a 2-sided test with an α of 0.05. Statistical analyses utilised SAS software v.9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patient demographic and disease characteristics

In total, 1502 patients enrolled with a by-country range of 217 patients (Germany) to 2 patients (Ireland) (Table 1).

Most patients were white (92.9%), male (61.1%), with a mean age of 60.9 years at hospital admission and with at least 1 documented co-morbidity at hospital admission, with diabetes (31.3%) and peripheral vascular disease (23.8%) being the most common. Moreover, 88.6% of patients were hospitalised with the primary reason of MRSA cSSTI treatment; ca. 50% were classified as community-acquired infections, although this percentage varied across countries. The most common infection types were extensive cellulitis (26.1%), surgical site infections or post-traumatic wounds (26.0%) and infected ulcers (24.7%). Surgical procedures for cSSTI management (incision and drainage, debridement) were required by 38.7% of patients.

3.2. Study hospital characteristics

Study investigators ($n = 341$) were located primarily at urban hospitals (91.2%; range 79.2–100% across countries) with a mean of 738.4 beds (39.9 critical care beds). Hospital size varied across countries (mean range of 315.7 beds per hospital in Slovakia to 947.6 beds in the UK).

Sites reporting antibiotic subcommittees or steering committees or i.v.-to-oral antibiotic switch protocols varied greatly across countries (across all sites: 82.9% reported antibiotic subcommittees or steering committees, 23.7% had i.v.-to-oral antibiotic switch protocols and 12.9% had ED protocols for MRSA cSSTI s) (Table 2). Cross-country comparisons showed a dynamic variability in the presence of ED protocols for MRSA cSSTI [Czech Republic lowest availability (0%); Spain highest (28.1%)].

Vancomycin (97.9%) and linezolid (93.5%) were the most common MRSA-active therapies available on hospital formularies. Restrictions on formulary (e.g. restricted to ID physicians, requirement for ID consult) were less frequent for vancomycin (14.4%) than linezolid (38.2%). In cross-country comparisons, Italy had the lowest percentage of formulary restrictions for vancomycin (2.6%) and linezolid (20.5%). The highest frequencies of vancomycin and linezolid formulary restrictions were in Greece (38.7%) and the UK (57.4%), respectively. The most cited formulary restrictions were need for approval from medical/specialised committee (vancomycin, 77.1%; linezolid, 68.0%), cost and insurance coverage (linezolid, 9.8%) and renal insufficiency (vancomycin, 14.6%). Linezolid was the most frequently listed antibiotic on MRSA cSSTI discharge protocols in all countries except Greece.

3.3. Patient-level meticillin-resistant S. aureus-active antibiotic treatment patterns

Of the 1502 patients, 1468 (97.7%) received confirmed MRSA-targeted therapy; most patients (81.5%) received i.v. therapy only (Table 3). Vancomycin was the most frequently used initial therapy in all countries [from 23.1% (Austria) to 69.8% (Portugal)]; the frequency of other antibiotics used varied across countries. Whilst vancomycin was still the most frequently used last therapy in all countries except Slovakia (where 45.0% of patients used fluoroquinolones), the proportion of patients using vancomycin dropped, while rates of linezolid use remained the same or increased in all countries compared with initial therapy.

In line with the cross-country variation in hospital antibiotic protocols, a large degree of variation was found in observed antibiotic treatment patterns across Europe. Only 10.7% of patients were switched from i.v. to oral antibiotic therapy while hospitalised (range: Greece, 2.0% to Spain, 20.2%). Medium to large country-level correlations were found between the proportion of sites with antibiotic subcommittees ($r = 0.66$, $P = 0.02$), i.v.-to-oral antibiotic switch protocols ($r = 0.42$, $P = 0.17$) and ED protocols ($r = 0.45$, $P = 0.14$) and rates of i.v.-to-oral antibiotic switch.

In total, 32.7% of patients were discharged from hospital on MRSA-targeted therapies (range: Portugal, 18.0% to Greece, 49.7%). Most patients (92.7%) received oral MRSA-targeted therapies upon discharge, with linezolid and clindamycin being the most commonly prescribed. Patients discharged from hospital on oral MRSA-targeted therapies received oral linezolid most frequently in France (51.4%), Germany (49.0%), Portugal (52.0%) and Spain (51.3%).

3.4. Actual length of intravenous therapy and hospital length of stay

The number of MRSA-targeted i.v. days ($P < 0.001$) and mean MRSA cSSTI hospital stay ($P < 0.001$) varied significantly across countries, with shortest i.v. days and LoS in the UK and longest in Poland and Portugal, respectively (Fig. 1). There was weak to no correlation between country-level mean i.v. days and proportion of sites with antibiotic subcommittees ($r = 0.08$, $P = 0.80$), i.v.-to-oral antibiotic switch protocols ($r = 0.20$, $P = 0.54$) or ED protocols ($r = -0.07$). Country-level mean LoS had a moderate negative correlation with the proportion of sites with antibiotic subcommittees ($r = -0.35$, $P = 0.26$) but weak correlations with the proportion with i.v.-to-oral antibiotic switch protocols ($r = 0.03$, $P = 0.92$) or ED protocols ($r = 0.03$, $P = 0.93$). Recurrence and re-admission due to MRSA cSSTI within 30 days post discharge were both <1%.

Table 1
Patient and disease characteristics.

	All countries ($N = 1502$)[a]	Austria ($n = 54$)	Czech Republic ($n = 41$)	France ($n = 261$)	Germany ($n = 217$)	Greece ($n = 151$)	Italy ($n = 190$)	Poland ($n = 43$)	Portugal ($n = 141$)	Slovakia ($n = 50$)	Spain ($n = 183$)	UK ($n = 169$)
Demographics												
Mean (S.D.) age (years)	60.9 (16.5)	68.8 (13.1)	65.2 (16.6)	58.4 (16.5)	62.5 (14.8)	60.6 (17.6)	55.4 (15.3)	54.4 (15.1)	62.4 (14.9)	62.2 (15.0)	65.6 (17.4)	60.0 (18.2)
Male [n (%)]	917 (61.1)	31 (57.4)	25 (61.0)	154 (59.0)	127 (58.5)	91 (60.3)	124 (65.3)	25 (58.1)	79 (56.0)	25 (50.0)	119 (65.0)	116 (68.6)
White [n (%)]	1395 (92.9)	52 (96.3)	41 (100.0)	221 (84.7)	210 (96.8)	149 (98.7)	179 (94.2)	43 (100.0)	133 (94.3)	50 (100.0)	180 (98.4)	135 (79.9)
Race/ethnicity unknown/not documented	16 (1.1)	1 (1.9)	0	12 (4.6)	3 (1.4)	0	0	0	0	0	0	0
Co-morbidities at hospital admission [n (%)][b]												
None documented/reported	286 (19.0)	1 (1.9)	8 (19.5)	49 (18.8)	29 (13.4)	32 (21.2)	66 (34.7)	2 (4.7)	21 (14.9)	2 (4.0)	31 (16.9)	45 (26.6)
Reported co-morbidities	1216 (81.0)	53 (98.1)	33 (80.5)	212 (81.2)	188 (86.6)	119 (78.8)	124 (65.3)	41 (95.3)	120 (85.1)	48 (96.0)	152 (83.1)	124 (73.4)
Diabetes	470 (31.3)	18 (33.3)	20 (48.8)	74 (28.4)	92 (42.4)	38 (25.2)	33 (17.4)	6 (14.0)	50 (35.5)	20 (40.0)	69 (37.7)	50 (29.6)
PVD	358 (23.8)	17 (31.5)	21 (51.2)	48 (18.4)	63 (29.0)	33 (21.9)	17 (8.9)	13 (30.2)	47 (33.3)	25 (50.0)	49 (26.8)	25 (14.8)
CPD	285 (19.0)	11 (20.4)	6 (14.6)	52 (19.9)	47 (21.7)	24 (15.9)	23 (12.1)	17 (39.5)	22 (15.6)	6 (12.0)	47 (25.7)	30 (17.8)
CHF	283 (18.8)	15 (27.8)	9 (22.0)	24 (9.2)	88 (40.6)	24 (15.9)	5 (2.6)	4 (9.3)	40 (28.4)	11 (22.0)	37 (20.2)	25 (14.8)
CAD (MI, CABG, etc.)	274 (18.2)	17 (31.5)	19 (46.3)	33 (12.6)	72 (33.2)	39 (25.8)	18 (9.5)	3 (7.0)	22 (15.6)	12 (24.0)	14 (7.7)	24 (14.2)
Renal disease, moderate/severe	169 (11.3)	10 (18.5)	10 (24.4)	21 (8.0)	46 (21.2)	13 (8.6)	5 (2.6)	2 (4.7)	28 (19.9)	10 (20.0)	13 (7.1)	11 (6.5)
Liver disease, mild	163 (10.9)	8 (14.8)	11 (26.8)	18 (6.9)	34 (15.7)	11 (7.3)	17 (8.9)	8 (18.6)	16 (11.3)	9 (18.0)	14 (7.7)	17 (10.1)
Infection characteristics [n (%)]												
Type of cSSTI												
Deep/extensive cellulitis	392 (26.1)	8 (14.8)	7 (17.1)	79 (30.3)	36 (16.6)	49 (32.5)	34 (17.9)	22 (51.2)	42 (29.8)	7 (14.0)	41 (22.4)	66 (39.1)
Surgical site infection or post-traumatic wound	390 (26.0)	11 (20.4)	15 (36.6)	57 (21.8)	60 (27.6)	39 (25.8)	58 (30.5)	7 (16.3)	41 (29.1)	27 (54.0)	44 (24.0)	31 (18.3)
Infected ulcer	371 (24.7)	24 (44.4)	11 (26.8)	50 (19.2)	57 (26.3)	30 (19.9)	48 (25.3)	4 (9.3)	38 (27.0)	4 (8.0)	70 (38.3)	35 (20.7)
Major abscess	265 (17.6)	10 (18.5)	7 (17.1)	66 (25.3)	52 (24.0)	20 (13.2)	26 (13.7)	8 (18.6)	15 (10.6)	11 (22.0)	20 (10.9)	32 (18.9)
Other (including infected burn)	84 (5.6)	1 (1.9)	1 (2.4)	12 (4.6)	12 (5.5)	13 (8.6)	24 (12.6)	2 (4.7)	5 (3.5)	1 (2.0)	8 (4.4)	5 (3.0)
Source of cSSTI[c]												
Community-acquired	749 (49.9)	32 (59.3)	11 (26.8)	122 (46.7)	94 (43.3)	94 (62.3)	74 (38.9)	22 (51.2)	104 (73.8)	4 (8.0)	110 (60.1)	81 (47.9)
Healthcare-associated	371 (24.7)	10 (18.5)	17 (41.5)	82 (31.4)	69 (31.8)	41 (27.2)	31 (16.3)	7 (16.3)	21 (14.9)	10 (20.0)	44 (24.0)	39 (23.1)
Hospital-acquired	81 (5.4)	2 (3.7)	4 (9.8)	4 (1.5)	11 (5.1)	8 (5.3)	3 (1.6)	2 (4.7)	11 (7.8)	3 (6.0)	22 (12.0)	10 (5.9)
Unknown/not documented	301 (20.0)	10 (18.5)	9 (22.0)	53 (20.3)	43 (19.8)	8 (5.3)	82 (43.2)	12 (27.9)	5 (3.5)	33 (66.0)	7 (3.8)	39 (23.1)
Surgical procedures related to cSSTI treatment[d]	582 (38.7)	18 (33.3)	20 (48.8)	85 (32.6)	101 (46.5)	67 (44.4)	37 (19.5)	26 (60.5)	88 (62.4)	27 (54.0)	73 (39.9)	40 (23.7)
Incision/drainage[e]	340 (58.4)	7 (38.9)	12 (60.0)	71 (83.5)	51 (50.5)	27 (40.3)	24 (64.9)	15 (57.7)	59 (67.0)	14 (51.9)	35 (47.9)	25 (62.5)
Amputation[e]	22 (3.8)	0	1 (5.0)	2 (2.4)	9 (8.9)	1 (1.5)	0	0	4 (4.5)	1 (3.7)	4 (5.5)	0
Debridement[e]	277 (47.6)	10 (55.6)	11 (55.0)	16 (18.8)	53 (52.5)	50 (74.6)	12 (32.4)	22 (84.6)	33 (37.5)	10 (37.0)	45 (61.6)	15 (37.5)
Other[e]	19 (3.3)	3 (16.7)	0	2 (2.4)	6 (5.9)	0	1 (2.7)	0	1 (1.1)	3 (11.1)	3 (4.1)	0
Sepsis/septic shock during cSSTI episode[f]	258 (17.2)	8 (14.8)	7 (17.1)	58 (22.2)	40 (18.4)	25 (16.6)	11 (5.8)	5 (11.6)	46 (32.6)	2 (4.0)	28 (15.3)	28 (16.6)
Infections during hospitalisation												
I.v. line infection	33 (2.2)	2 (3.7)	1 (2.4)	3 (1.1)	4 (1.8)	9 (6.0)	0	4 (9.3)	4 (2.8)	0	1 (0.5)	5 (3.0)
Superinfection	84 (5.6)	4 (7.4)	1 (2.4)	13 (5.0)	12 (5.5)	6 (4.0)	3 (1.6)	7 (16.3)	23 (16.3)	3 (6.0)	7 (3.8)	5 (3.0)

S.D., standard deviation; PVD, peripheral vascular disease; CPD, chronic pulmonary disease; CHF, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; cSSTI, complicated skin and soft-tissue infection; i.v., intravenous.

[a] All countries ($N = 1502$) includes 2 patients from Ireland; however, data from Ireland were not reported separately owing to the small sample size.

[b] Patients could have more than 1 co-morbidity; country-specific data for the top seven co-morbidities overall are presented.

[c] Healthcare-associated: hospitalisation in past 90 days, residence in nursing home or extended care facility, treatment with chronic haemodialysis, or receipt of home healthcare or wound care; hospital-acquired: >48 h after hospital admission.

[d] Patients could have more than one surgical procedure.

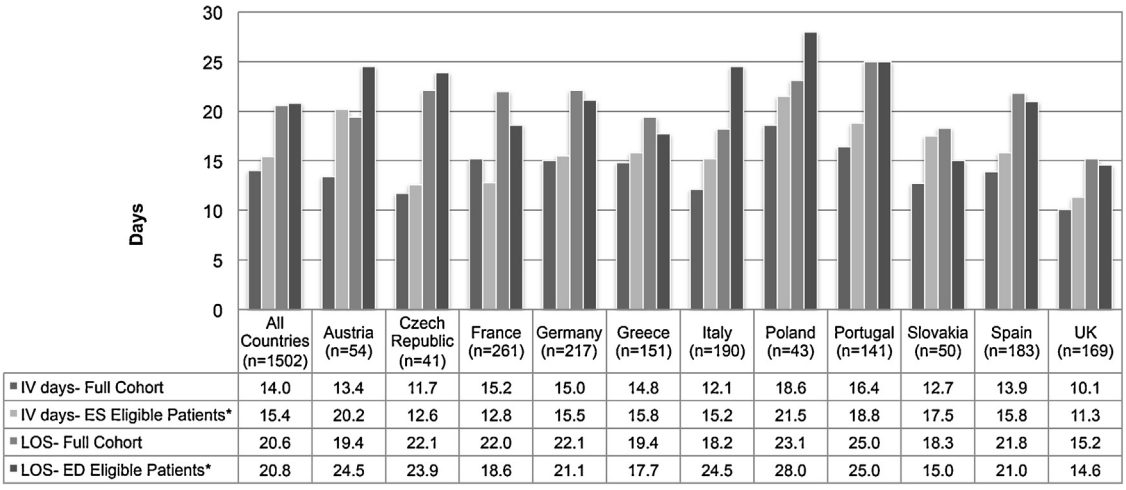
[e] Percentages calculated from a denominator of 'surgical procedures related to cSSTI treatment'.

[f] Severe sepsis/septic shock at any time during the hospital stay.

Table 2
Percentage of hospitals with antibiotic subcommittees and early switch and early discharge (ED) protocols.

	Antibiotic subcommittee or steering committee (%)	I.v.-to-oral antibiotic switch protocol (%)	ED protocol for MRSA cSSTI (oral or OPAT) (%)
All hospitals ($N = 341$)[a]	82.9	23.7	12.9
Austria ($n = 24$)	87.5	4.1	4.1
Czech Republic ($n = 10$)	80.0	10.0	0
France ($n = 48$)	91.6	20.8	4.1
Germany ($n = 50$)	66.0	18.0	12.0
Greece ($n = 33$)	96.9	12.1	9.0
Italy ($n = 39$)	43.5	12.8	7.6
Poland ($n = 19$)	94.7	47.3	5.2
Portugal ($n = 20$)	85.0	0	25.0
Slovakia ($n = 7$)	100.0	71.4	14.2
Spain ($n = 32$)	96.8	37.5	28.1
UK ($n = 58$)	93.1	43.1	22.4

I.v., intravenous; MRSA, meticillin-resistant *Staphylococcus aureus*; cSSTI, complicated skin and soft-tissue infection; OPAT, outpatient parenteral antibiotic therapy.
[a] All hospitals ($N = 341$) includes 1 location in Ireland; however, data from Ireland were not reported separately owing to the small sample size.



	All Countries (n=1502)	Austria (n=54)	Czech Republic (n=41)	France (n=261)	Germany (n=217)	Greece (n=151)	Italy (n=190)	Poland (n=43)	Portugal (n=141)	Slovakia (n=50)	Spain (n=183)	UK (n=169)
IV days- Full Cohort	14.0	13.4	11.7	15.2	15.0	14.8	12.1	18.6	16.4	12.7	13.9	10.1
IV days- ES Eligible Patients*	15.4	20.2	12.6	12.8	15.5	15.8	15.2	21.5	18.8	17.5	15.8	11.3
LOS- Full Cohort	20.6	19.4	22.1	22.0	22.1	19.4	18.2	23.1	25.0	18.3	21.8	15.2
LOS- ED Eligible Patients*	20.8	24.5	23.9	18.6	21.1	17.7	24.5	28.0	25.0	15.0	21.0	14.6

Fig. 1. Observed intravenous (i.v.) days and length of stay (LoS) from complicated skin and soft-tissue infection index date. * The number of early switch (ES)- and early discharge (ED)-eligible patients is a subset of the sample sizes listed by country. All countries ($N = 1502$) includes 2 patients from Ireland; however, data from Ireland were not reported separately owing to the small sample size.

3.5. Potential opportunities for early switch and early discharge and potential savings in intravenous days, hospital length of stay and costs

All countries exhibited potential opportunities for ES or ED compared with observed actual treatment patterns. The proportion of patients meeting key ES criteria varied across countries (range: Slovakia, 12.0% to Greece, 56.3%) (Table 4). Among ES-eligible patients, mean actual i.v. days ranged from 11.3 ± 6.2 days (UK) to 21.5 ± 9.4 days (Poland) (Fig. 1); following ES criteria could result in potential i.v. line-days saved (mean ± S.D. range: Slovakia, 2.7 ± 1.9 days to Spain, 7.2 ± 8.5 days) (Table 4). The proportion of patients meeting key ED criteria varied across countries, ranging from 10.0% (Slovakia) to 48.2% (Portugal) (Table 4). Among ED-eligible patients, average actual LoS ranged from 14.6 ± 8.8 days (UK) to 28.0 ± 9.4 days (Poland) (Fig. 1); following ED criteria could result in potential bed-days saved (mean ± S.D. range: Slovakia, 1.2 ± 0.4 days to France, 7.8 ± 10.6 days) (Table 4). Potential cost savings per patient meeting ED criteria ranged from an estimated €414 (Slovakia) to €2703 (France) when applying the cross-country average cost per bed-day of €344.87 to all patients (Table 4).

4. Discussion

This study may provide the first published data on pan-European real-world hospital protocols and treatment patterns for MRSA cSSTI with ca. 1500 patients hospitalised in 12 European countries. Overall, i.v. vancomycin was the most common initial treatment for MRSA cSSTI in most countries evaluated; oral linezolid was the drug of choice for MRSA cSSTI at hospital discharge. The majority of patients in all countries were treated only with i.v. therapy, with ca. 10% of patients switched from i.v. to oral antibiotic therapy while hospitalised. There were moderate to strong correlations between the country-level proportion of sites with antibiotic subcommittees and i.v.-to-oral antibiotic switch and/or ED protocols and the proportion of patients with an i.v.-to-oral antibiotic switch, suggesting that the presence of structures to support stewardship activity may be drivers for more ES and potentially ED. However, this may depend on the actual implementation of these protocols, which was not captured by this study; we could not determine the level of clinician awareness regarding such activity. Overall, these results show substantial opportunities to decrease i.v. antibiotic treatment days and hospital LoS by switching patients from i.v. to oral antibiotic therapy.

The variability in treatment administration patterns and hospital LoS observed across countries may be due to a number of reasons, including differences in physician and patient expectations and different healthcare systems among the countries evaluated [17]. For example, i.v.-to-oral antibiotic switch rate variability may be affected by different perceptions on whether oral antibiotics represent the standard of care for treating serious infections [18,19]. These perceptions may partly explain the noted

Table 3
Country-specific antibiotic treatment patterns.

	All countries ($N = 1502$)[a]	Austria ($n = 54$)	Czech Republic ($n = 41$)	France ($n = 261$)	Germany ($n = 217$)	Greece ($n = 151$)	Italy ($n = 190$)	Poland ($n = 43$)	Portugal ($n = 141$)	Slovakia ($n = 50$)	Spain ($n = 183$)	UK ($n = 169$)
MRSA-active therapy [*n* (%)]	1468 (97.7)	52 (96.3)	40 (97.6)	258 (98.9)	215 (99.1)	149 (98.7)	187 (98.4)	38 (88.4)	139 (98.6)	40 (80.0)	179 (97.8)	169 (100.0)
I.v.-to-oral switch	161 (10.7)	2 (3.7)	3 (7.3)	46 (17.6)	14 (6.5)	3 (2.0)	9 (4.7)	2 (4.7)	8 (5.7)	10 (20.0)	37 (20.2)	27 (16.0)
I.v. only	1224 (81.5)	46 (85.2)	28 (68.3)	189 (72.4)	192 (88.5)	141 (93.4)	168 (88.4)	36 (83.7)	126 (89.4)	30 (60.0)	138 (75.4)	128 (75.7)
Oral only	12 (0.8)	1 (1.9)	1 (2.4)	3 (1.1)	1 (0.5)	0	0	0	0	1 (2.0)	4 (2.2)	1 (0.6)
I.v. and oral inpatient	49 (3.3)	4 (7.4)	8 (19.5)	13 (5.0)	6 (2.8)	1 (0.7)	2 (1.1)	0	0	0	2 (1.1)	13 (7.7)
OPAT at discharge	34 (2.3)	0	1 (2.4)	10 (3.8)	3 (1.4)	4 (2.6)	8 (4.2)	0	5 (3.5)	0	2 (1.1)	1 (0.6)
Initial MRSA therapy among patients with MRSA-active therapy [*n* (%)][b,c]												
Vancomycin	737 (50.2)	12 (23.1)	21 (52.5)	162 (62.8)	115 (53.5)	43 (28.9)	78 (41.7)	17 (44.7)	97 (69.8)	14 (35.0)	87 (48.6)	90 (53.3)
Linezolid	222 (15.1)	10 (19.2)	3 (7.5)	49 (19.0)	22 (10.2)	31 (20.8)	24 (12.8)	1 (2.6)	28 (20.1)	0	43 (24.0)	11 (6.5)
Clindamycin	159 (10.8)	9 (17.3)	6 (15.0)	13 (5.0)	34 (15.8)	35 (23.5)	10 (5.3)	9 (23.7)	4 (2.9)	8 (20.0)	19 (10.6)	12 (7.1)
Teicoplanin	153 (10.4)	4 (7.7)	1 (2.5)	21 (8.1)	8 (3.7)	19 (12.8)	43 (23.0)	0	1 (0.7)	0	7 (3.9)	48 (28.4)
Fluoroquinolones[d]	106 (7.2)	2 (3.8)	1 (2.5)	23 (8.9)	17 (7.9)	20 (13.4)	10 (5.3)	6 (15.8)	1 (0.7)	13 (32.5)	9 (5.0)	4 (2.4)
Daptomycin	87 (5.9)	6 (11.5)	0	4 (1.6)	11 (5.1)	22 (14.8)	20 (10.7)	0	0	1 (2.5)	14 (7.8)	9 (5.3)
Rifampicin	62 (4.2)	2 (3.8)	6 (15.0)	32 (12.4)	10 (4.7)	1 (0.7)	4 (2.1)	0	0	0	1 (0.6)	6 (3.6)
Tigecycline	48 (3.3)	9 (17.3)	0	3 (1.2)	11 (5.1)	5 (3.4)	10 (5.3)	0	2 (1.4)	0	7 (3.9)	1 (0.6)
SXT	45 (3.1)	0	10 (25.0)	5 (1.9)	5 (2.3)	0	1 (0.5)	6 (15.8)	10 (7.2)	3 (7.5)	5 (2.8)	0
Other[e]	44 (3.0)	3 (5.8)	0	15 (5.8)	5 (2.3)	4 (2.7)	1 (0.5)	2 (5.3)	0	1 (2.5)	1 (0.6)	12 (7.1)
Last MRSA therapy among patients with MRSA-active therapy [*n* (%)][b,c]												
Vancomycin	609 (41.5)	11 (21.2)	21 (52.5)	127 (49.2)	96 (44.7)	41 (27.5)	71 (38.0)	18 (47.4)	82 (59.0)	10 (25.0)	59 (33.0)	72 (42.6)
Linezolid	310 (21.1)	10 (19.2)	4 (10.0)	73 (28.3)	42 (19.5)	41 (27.5)	27 (14.4)	2 (5.3)	33 (23.7)	1 (2.5)	54 (30.2)	23 (13.6)
Teicoplanin	158 (10.8)	4 (7.7)	1 (2.5)	23 (8.9)	13 (6.0)	18 (12.1)	44 (23.5)	0	5 (3.6)	0	6 (3.4)	43 (25.4)
Clindamycin	141 (9.6)	9 (17.3)	5 (12.5)	18 (7.0)	26 (12.1)	21 (14.1)	10 (5.3)	7 (18.4)	2 (1.4)	7 (17.5)	23 (12.8)	13 (7.7)
Fluoroquinolones[d]	110 (7.5)	2 (3.8)	0	27 (10.5)	13 (6.0)	16 (10.7)	10 (5.3)	6 (15.8)	2 (1.4)	18 (45.0)	14 (7.8)	2 (1.2)
Daptomycin	98 (6.7)	6 (11.5)	0	6 (2.3)	17 (7.9)	24 (16.1)	22 (11.8)	0	1 (0.7)	1 (2.5)	13 (7.3)	8 (4.7)
Rifampicin	60 (4.1)	2 (3.8)	5 (12.5)	30 (11.6)	8 (3.7)	1 (0.7)	4 (2.1)	0	0	0	5 (2.8)	5 (3.0)
SXT	56 (3.8)	0	9 (22.5)	6 (2.3)	5 (2.3)	0	4 (2.1)	8 (21.1)	10 (7.2)	2 (5.0)	12 (6.7)	0
Tigecycline	54 (3.7)	10 (19.2)	0	2 (0.8)	10 (4.7)	7 (4.7)	10 (5.3)	0	4 (2.9)	0	10 (5.6)	1 (0.6)
Others[e]	58 (4.0)	3 (5.8)	0	11 (4.3)	6 (2.8)	4 (2.7)	1 (0.5)	1 (2.6)	6 (4.3)	1 (2.5)	1 (0.6)	24 (14.2)
Discharge MRSA therapy [*n* (%)]	480 (32.7)	15 (28.8)	9 (22.5)	107 (41.5)	51 (23.7)	74 (49.7)	40 (21.4)	10 (26.3)	25 (18.0)	14 (35.0)	80 (44.7)	54 (32.0)
OPAT[f]	35 (7.3)	0	1 (11.1)	10 (9.3)	3 (5.9)	5 (6.8)	8 (20.0)	0	5 (20.0)	0	2 (2.5)	1 (1.9)
Oral[f]	445 (92.7)	15 (100.0)	8 (88.9)	97 (90.7)	48 (94.1)	69 (93.2)	32 (80.0)	10 (100.0)	20 (80.0)	14 (100.0)	78 (97.5)	53 (98.1)
Discharge therapy [*n* (%)]												
Linezolid[f]	202 (42.1)	5 (33.3)	2 (22.2)	56 (52.3)	26 (51.0)	29 (39.2)	8 (20.0)	0	13 (52.0)	0	43 (53.8)	20 (37.0)
Clindamycin[f]	95 (19.8)	6 (40.0)	3 (33.3)	8 (7.5)	15 (29.4)	21 (28.4)	10 (25.0)	2 (20.0)	0	2 (14.3)	14 (17.5)	13 (24.1)
Fluoroquinolones[d,f]	67 (14.0)	1 (6.7)	0	11 (10.3)	5 (9.8)	19 (25.7)	7 (17.5)	4 (40.0)	1 (4.0)	9 (64.3)	10 (12.5)	0
SXT[f]	57 (11.9)	0	3 (33.3)	11 (10.3)	2 (3.9)	7 (9.5)	7 (17.5)	4 (40.0)	5 (20.0)	1 (7.1)	16 (20.0)	0
Rifampicin[f]	34 (7.1)	1 (6.7)	0	10 (9.3)	2 (3.9)	6 (8.1)	3 (7.5)	0	0	0	8 (10.0)	4 (7.4)
Teicoplanin[f]	14 (2.9)	0	0	4 (3.7)	0	1 (1.4)	8 (20.0)	0	0	0	0	1 (1.9)
Vancomycin[f]	11 (2.3)	0	0	4 (3.7)	1 (2.0)	1 (1.4)	0	0	5 (20.0)	0	0	0
Tigecycline[f]	2 (0.4)	0	0	0	0	0	0	0	0	0	0	0
Daptomycin[f]	1 (0.2)	0	0	1 (0.9)	0	0	0	0	0	0	0	0
Other[e,f]	54 (11.3)	3 (20.0)	0	13 (12.1)	1 (2.0)	7 (9.5)	2 (5.0)	0	1 (4.0)	2 (14.3)	2 (2.5)	23 (42.6)

MRSA, meticillin-resistant *Staphylococcus aureus*; i.v., intravenous; OPAT, outpatient parenteral antibiotic therapy; SXT, trimethoprim/sulfamethoxazole.

[a] All countries ($N = 1502$) includes 2 patients from Ireland; however, data from Ireland were not reported separately owing to the small sample size.

[b] Drug groups are not mutually exclusive; multiple medications could be used simultaneously.

[c] Percentages calculated from a denominator based on number of patients with 'MRSA-active therapy'.

[d] Fluoroquinolones included ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin.

[e] Other antibiotics included doxycycline, ertapenem, fusidic acid, gentamicin, imipenem, meropenem, minocycline, pristinamycin, quinupristin/dalfopristin and trimethoprim.

[f] Percentages calculated from a denominator based on number of patients from 'discharge MRSA therapy'.

Table 4
Early switch (ES) and early discharge (ED) eligibility and potential savings in intravenous (i.v.) days, hospital length of stay and costs.

	Patient opportunities for ES		Patient opportunities for ED		Potential cost savings due to bed-days saved	
	ES-eligible (%)	Potential i.v. days saved by ES-eligible patients (mean ± S.D.)	ED-eligible (%)	Potential bed-days saved by ED-eligible patients (mean ± S.D.)	Average cost (€344.87 per bed-day)[a]	Country-specific costs (2012€)[a,b]
All countries (n = 1502)[c]	33.6	6.0 ± 5.5	37.9	6.2 ± 8.2	2135 ± 2829	2129 ± 2846
Austria (n = 54)	25.9	6.9 ± 5.0	33.3	6.1 ± 5.9	2088 ± 2023	2716 ± 2631
Czech Republic (n = 41)	22.0	3.3 ± 2.1	46.3	5.3 ± 6.5	1833 ± 2247	1495 ± 1832
France (n = 261)	28.4	5.3 ± 4.1	35.2	7.8 ± 10.6	2703 ± 3643	2864 ± 3861
Germany (n = 217)	46.5	6.7 ± 6.0	47.0	4.2 ± 5.5	1454 ± 1912	1683 ± 2214
Greece (n = 151)	56.3	6.6 ± 6.0	41.1	7.5 ± 10.6	2581 ± 3644	2317 ± 3272
Italy (n = 190)	25.3	5.7 ± 4.3	34.2	7.0 ± 8.1	2430 ± 2785	2642 ± 3028
Poland (n = 43)	32.6	6.6 ± 5.5	27.9	6.6 ± 6.4	2270 ± 2203	1235 ± 1199
Portugal (n = 141)	42.6	5.2 ± 4.2	48.2	6.4 ± 7.1	2216 ± 2445	1592 ± 1756
Slovakia (n = 50)	12.0	2.7 ± 1.9	10.0	1.2 ± 0.4	414 ± 154	320 ± 119
Spain (n = 183)	26.2	7.2 ± 8.5	38.8	6.7 ± 9.1	2327 ± 3136	2193 ± 2955
UK (n = 169)	26.6	5.0 ± 4.9	32.5	4.3 ± 5.9	1499 ± 2024	1872 ± 2528

S.D., standard deviation.
[a] Cost per bed-day units in euros. Costs were applied at a patient-level (e.g. person-level bed-days saved × cost per bed-day), which resulted in mean costs that are slightly different than multiplying average bed-days saved by cost per bed-day.
[b] Costs per country: average across countries, €344.87 (used for the main cohort); Austria, €448.59; Czech Republic, €281.24; France, €365.51; Germany, €399.27; Greece, €309.65; Italy, €375.02; Poland, €187.61; Portugal, €247.70; Slovakia, €266.85; Spain, €325.01; and UK, €430.70 (Appendix).
[c] All countries (N = 1502) includes 2 patients from Ireland; however, data from Ireland were not reported separately owing to the small sample size.

practice variations despite the availability of modern oral formulations that are highly bioavailable with good safety profiles [17] and equivalent effectiveness [20,21]. Moreover, oral MRSA-active drugs have been implemented in recent algorithms and guidelines for treatment of MRSA cSSTI, further supporting the use of these agents [22–24]. The extent and severity of the infections may have contributed to reluctance to switch patients from i.v. to oral formulations or to discharge patients sooner. Of note, in the current patient population, 17.2% of patients developed severe sepsis/septic shock at any time during the hospital stay, and ca. 70% had more complicated infections such as deep cellulitis, abscess or ulcer. This is higher than the 4–6% of patients with sepsis in trials of antibiotic treatment of cSSTI with or without microbiological evidence of MRSA [21,25]. In addition, patients in this real-world study were older and had more baseline co-morbidities compared with typical clinical trial populations [26]. Although we were unable to assess extent and severity using lesion size in this retrospective study, as is done in a clinical trial, the current population were all MRSA-confirmed cSSTI, which is considered a more severe population than more recent trials assessing the broader indication of acute bacterial skin and skin-structure infections with only MRSA subpopulations present [26].

One strength of this data set is that it was collected in a consistent manner across countries, which makes it possible to evaluate differences throughout Europe. However, we accept that the case-mix in the different hospital populations was not uniform and may make benchmarking difficult. This study fills a gap in the literature by providing practice pattern data for each country included together with patient clinical and demographic characteristics. In addition, differences in living conditions, infrastructure of outpatient treatment, usual treatment behaviours and culture, and healthcare system economics may also contribute to the observed differences across countries. Incentives and barriers for discharge and reimbursement are likely significant drivers for the differences observed.

In comparison with the typical real-world US LoS for cSSTI of ca. 5 days [27] where there are strong incentives to minimise hospital days, the typical LoS in this observational European study was ca. 20 days in an MRSA-specific population. These differences in LoS by region have also been confirmed in a phase 4 MRSA cSSTI clinical trial [13], with the USA having a LoS of ca. 4–5 days while Europe had a LoS of ca. 13–15 days. The long LoS in the current study may have resulted in the low 30-day post-discharge recurrence (<1%) and re-admission (<1%) rates due to MRSA cSSTI, coupled with the potential limitation in follow-up data availability if patients were re-admitted to a different hospital. In the USA, 30-day re-admission rates for cSSTI are significant at 7–13% for cSSTI in retrospective observational analyses [28].

Limitations of this study include the retrospective observational design in the calculation of potential country cost savings with application to ES and ED criteria. To verify the findings, a prospective trial should test the effect of implementing defined ES and ED criteria, or a controlled cohort study could compare the same hospitals before and after the implementation of such criteria. However, such studies may not be practical or economical given the complexities of such a multinational study. For this reason, the most pragmatic method to capture current practice patterns across many countries was likely a retrospective design to avoid bias in physician behaviours (Hawthorne effect) when prospective data collection was occurring. Despite these limitations, real-world data are increasingly recognised as a critical piece of information in healthcare decision-making, particularly when evaluating practical aspects of implementing ES and ED protocols and systems that are functional and easy to use.

In this study, countries did not contribute data equally [ca. 70% of patients came from 5 Western European countries (France,

Germany, Italy, Spain and the UK)]. However, this data collection pattern may actually reflect the epidemiology and burden of MRSA cSSTI across Europe. The countries that contributed data on fewer patients (e.g. Austria, Slovakia, Poland and Czech Republic) indicated having fewer MRSA cSSTI cases to screen for inclusion, which was consistent with their published epidemiology reporting MRSA rates of 7–14%. In contrast, MRSA rates in the 5 Western European countries heavily represented in this study have been reported to be ≥25% [25], and these 5 European countries exhibited some of the most significant opportunities to reduce i.v. line days and hospital LoS and achieve potential savings of €1500 to >€2400 per ED-eligible patient. Interestingly, in other countries, we found the highest opportunity for ED (41% of patients with MRSA cSSTI in Greece, facing severe economic crisis and austerity measures, with rates of MRSA of >40% [25]) could have been discharged sooner using a criteria-based approach with significant potential cost savings (>€2500 per ED-eligible patient). This exemplifies the value of the country-level data that could, together with local decision factors, influence local patterns in allocating limited resources most effectively. Whilst this study focused on MRSA cSSTI, a similar criteria-based approach for other infections or diseases could provide opportunities to improve economic outcomes.

In conclusion, this large study is the first to document differences in actual treatment patterns of hospitalised patients with MRSA cSSTI among European countries. Wide variation in treatment patterns and resource utilisation occurred across countries. Evidence supports a correlation between the availability of local antibiotic stewardship activity, such as ES and ED protocols, and increased likelihood of reduced hospital LoS. Furthermore, using well-accepted ES and ED criteria, significant opportunities for certain patients to be switched from i.v. to oral antibiotic therapy and discharged home from the hospital sooner were identified.

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Competing interests: DN has received lecture fees, travel support for attending meetings and fees for advisory boards from Astellas, Astra-Zeneca, Bayer, Durata and Pfizer Inc.; CE has received lecture fees, travel support for attending meetings and fees for advisory boards from Astra-Zeneca, Bayer, Cubist, Durata and Pfizer Inc.; WL has received support for attending meetings, travel support and fees for advisory boards from Astellas and Pfizer Inc.; JMS and CTS are employees of Pharmerit International, who were paid consultants to Pfizer in connection with this study; CM is an employee of Medical Data Analytics, a subcontractor to Pharmerit International for this project; DS, CC, PH, RC, JZL and SH are employees of Pfizer Inc.

Ethical approval: Ethical approval was obtained by study investigator physicians when required in various countries for collection of anonymous, de-identified medical chart data and complied with each country's specific data privacy laws.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2014.04.007.

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